Applicant amends the application to correct this. These changes do not narrow the scope of the claims, and are not done to overcome any bar to patentability. To the contrary, they simply correct a typographical error. The United States Supreme Court, in *Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002), ruled that these kinds of changes do not alter the legitimate scope of the claims under the doctrine of equivalents.

Obviousness

Claims 1-19 are pending. All claims stand rejected as obvious over Mark W. GRINSTAFF *et al., Methods for In Vivo Delivery…*, United States Letters Patent No. 5,560,156 combined with John E. HOOVER *et al., Remington's Pharmaceutical Sciences* pp. 956-71 (18th ed., 1990).

Reconsideration is respectfully requested because these references fail to establish a *prima facie* case of obviousness. We first briefly recapitulate Grinstaff and the claimed invention, and then explain how Grinstaff fails to support a *prima facie* case.

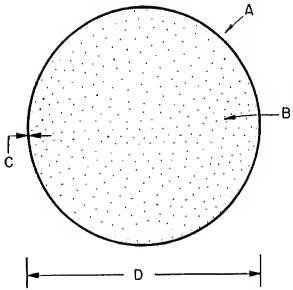
Hydrocortisone 17-Butyrate Is Recognized In
The Art As A Topical Skin Medicine To Treat
Eczemas And Other Skin Conditions

Hydrocortisone 17-butyrate is a topical steroidal anti-inflammatory agent. *See* Pravin M. Patel, *Declaration Under 37 C.F.R. § 1.132* (December, 2007). It is used topically. *Id.* It is commercially available in The United States

as a topical cream, a topical lotion, a topical ointment, and a topical solution. *Id.* It is not available in the United States in any non-topical formulation. *Id.* To the contrary, The Federal Food, Drug & Cosmetics Act currently prohibits marketing hydrocortisone 17-butyrate in any non-topical formulation. *Id.*

Grinstaff Teaches A Blood Substitute

The Examiner correctly notes that Grinstaff teaches a "hemoglobin microsphere," a new artificial oxygen-transmitting blood cell. Grinstaff at 3:10 *et seq.* notes the need in the art for an oxygen-carrying red blood cell substitute. Grinstaff also notes that many chemotherapeutic agents require oxygen to work well. Grinstaff at 6:28 *et seq.* thus teaches to make an oxygen-transmitting polymeric shell using the protein hemoglobin. The shell A is made in a thickness C, and is filled with an "interior fill" B.



These shells have "surprisingly high oxygen-binding capability." *Id.* at 16:47. They are thus suitable as a blood substitute. *See e.g.*, 19:53 *et seq.*

The Examiner correctly notes that Grinstaff teaches that the interior fill for these shells may be a solution of a fluorocarbon or a bio-compatible oil such

as safflower oil, 26:15, and an intravenous drug, *see* 26:21-31. Given the shells' high oxygen-binding capability, these shells would appear useful for intravenous administration of any of the various intravenous cytotoxic drugs which require oxygen to work well (*e.g.*, vinblastine, vincristine, cyclophosphamide, melphalan).

While Grinstaff enumerates many drugs potentially suitable for inclusion in the interior fill, *see e.g.*, 26:21-31; 26:45-51; the Examiner correctly notes that Grinstaff fails to suggest hydrocortisone 17-butyrate. This is not surprising because Grinstaff teaches an intravenous blood substitute, while hydrocortisone 17-butyrate is not recognized in the art as being acceptable for intravenous administration.

Grinstaff Combined With Hoover Fails To Support
A *Prima Facie* Case Of Obviousness

A *prima facie* case of obviousness requires three elements: (1) the prior art must teach each claim limitation; (2) the prior art must provide some suggestion or motivation to combine the references; and (3) the prior art must teach a reasonable expectation of success. *See e.g., In re Vaeck*, 947 F.2d 488, (Fed. Cir., 1991).

In the instant case, Grinstaff combined with Hoover fails to support a *prima facie* case of obviousness because (1) the prior art fails to teach each claim limitation; (2) the prior art fails to provide some suggestion or motivation to

combine the references; and (3) the prior art teaches a reasonable expectation of *failure*, not success. We discuss each in turn.

the art of record fails to teach each claim limitation

The Art Of Record Fails To Teach Hydrocortisone 17-Butyrate

A *prima facie* case of obviousness requires the prior art to teach each and every claim limitation. *See e.g., In re Vaeck*, 947 F.2d 488, (Fed. Cir., 1991).

In the instant case, the claims require hydrocortisone 17-butyrate. The Examiner correctly notes that neither Grinstaff nor Hoover teach hydrocortisone 17-butyrate. The *Office Action* accordingly fails to state a *prima facie* case of obviousness.

The Art Of Record Fails To Teach A Method For Stabilizing Hydrocortisone 17-Butyrate

The instant application, at *e.g.*, 2:5-9, teaches that hydrocortisone 17-butyrate is thermodynamically unstable under normal storage conditions and is therefore prone to degrade into hydrocortisone 21-butyrate. The inventor claims a method for stabilizing hydrocortisone 17-butyrate by combining it with an omega-6 acid. The specification explains that stabilization is preferably done with "an amount which is at least equimolar."

The Examiner correctly recognizes that Grinstaff at 26:6-31 teaches to mix oil-soluble cytotoxic drugs, nonsteroidal anti-inflammatory agents, steroids, and/or immunosuppressive agents in a fluorocarbon, soybean oil, safflower oil,

coconut oil, olive oil, cotton seed oil or other biocompatible oil. The Examiner correctly recognizes that Grinstaff fails to teach that the bio-compatible oil must contain an omega-6 acid(s) and must contain these in an amount which would be sufficient to stabilize hydrocortisone 17-butyrate.

Applicant understands the Examiner to conclude that Grinstaff's mention of safflower oil inherently teaches omega-6 acid in an amount sufficient to stabilize hydrocortisone 17-butyrate. Applicant respectfully notes that the legal standard is somewhat different.

To inherently anticipate a claim limitation, the claimed limitation must inevitably and *necessarily* flow from the prior art structure. *See e.g., In re Oelrich*, 666 F.2d 578, 581-82 (C.C.P.A., 1981). Thus, the record must include objective evidence that the prior art structure "*necessarily*" produces the claimed limitation. *See Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (B.P.A.I., 1990) (emphasis in original).

In the instant case, the Examiner correctly notes that Grinstaff teaches to use a number of bio-compatible oils, either alone or in combination. To inherently anticipate the claims, Grinstaff's oils must inevitably and necessarily have omega-6 acid and must inevitably and necessarily stabilize hydrocortisone 17-butyrate. *See e.g., In re Oelrich*, 666 F.2d 578, 581-82 (C.C.P.A., 1981). The record has no evidence, however, that each of Grinstaff's oils contains omega-6

acid. Applicant respectfully notes that several of Grinstaff's oils (*e.g.*, fluorocarbons, coconut oil) do not have any omega-6 acid at all.

The art of record fails to provide a motivation to combine hydrocortisone 17-butyrate with Grinstaff's polymer shells

The prior art must provide some suggestion or motivation to make the claimed modification. *See e.g., In re Vaeck*, 947 F.2d 488, (Fed. Cir., 1991). The Examiner correctly recognizes that neither Grinstaff nor Hooper expressly suggest combining hydrocortisone 17-butyrate in Grinstaff's micro spheres.

The Examiner, however, correctly recognizes that a reference need not suggest the combination *in haec verba*. The reference need only suggest the desirability of the claimed invention when read as a whole. *E.g., In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir., 1998). This desirability may come from any of three possible sources: (1) the teachings of the prior art; (2) the knowledge of one of ordinary skill in the art; or (3) the nature of the problem to be solved. *Id.*

In the instant case, the art of record fails to suggest any desirability. To the contrary, the art of record *discourages* the combination.

The *Office Action* proposes that one of skill in the art would have been motivated to deliver hydrocortisone 17-butyrate in Grinstaff's microcapsule system because "It would be reasonably expected that hydrocortisone butyrate is even less soluble than hydrocortisone itself."

Applicant respectfully requests reconsideration because the art of record fails to teach the relative solubility of hydrocortisone 17-butyrate and of hydrocortisone. While Applicant respects the Examiner's scientific experience, Applicant respectfully notes that if relative solubility is the basis for this rejection, then the Board of Appeals will require some factual evidence showing the compounds' relative solubility.

Furthermore, the art of record fails to teach why relative solubility (in water? in safflower oil? in any oil?) is germane to claims which are not limited by any particular solubility, but by omega-6 acid content. Put another way, assuming that hydrocortisone 17-butyrate is less soluble in a particular solvent than is hydrocortisone, why does this matter? How does this make it more advantageous to put a topical drug like hydrocortisone 17-butyrate in Grinstaff's micro spheres? The *Office Action* fails to say.

In this regard, the *Office Action* is similar to ***In re Jones***, 958 F.2d 347 (Fed. Cir., 1992). In *Jones*, the inventor claimed a particular ethanol salt of dicamba. The prior art did not teach the particular salt claimed. One reference, however, taught substituted ammonium salts of dicamba, and another reference taught how to make ethanol salts. The Court Of Appeals reversed the obviousness rejection, finding that the prior art failed to teach any advantage in the claimed dicamba ethanol salt. In the instant case, as in *Jones*, the prior art fails to teach any

particular advantage to be gained by combining hydrocortisone 17-butyrate with Grinstaff's micro spheres.

The Examiner also says that one would have been motivated to deliver hydrocortisone 17-butyrate in Grinstaff's microcapsule system because "substituting a compound with the ester of that compound is obvious."

Applicant agrees that as a general principle, substituting interchangeable equivalents is obvious. In the instant case, however, the evidence of record shows that hydrocortisone is not interchangeable with hydrocortisone 17-butyrate. For example, hydrocortisone 17-butyrate is approved only for topical administration. *See DEC.* In contrast, hydrocortisone is approved for systemic administration as an intramuscular injection, as an enema and as an oral dosage. *See* Hoover at 965. The art of record cautions that while hydrocortisone may also be administered topically, "Systemic side effects can result from topical application." *Id.*

Similarly, the evidence of record shows that hydrocortisone 17-butyrate degrades to hydrocortisone 21-butyrate. No evidence shows that hydrocortisone degrades into hydrocortisone 21-butyrate. Applicant respectfully notes that hydrocortisone lacks a butyrate moiety. Applicant thus infers that hydrocortisone would not be expected to degrade into hydrocortisone 21-butyrate, nor into any other butyrate form.

Similarly, the evidence of record shows that omega-6 acid stabilizes hydrocortisone 17-butyrate. No evidence shows that omega-6 acid stabilizes hydrocortisone. Applicant infers that omega-6 may indeed stabilize hydrocortisone, but this is speculation; this fact would need to be established by evidence of record before it could support an allegation that hydrocortisone 17-butyrate and hydrocortisone are obviously interchangeable.

Applicant thus respectfully believes that the evidence of record fails to show that hydrocortisone 17-butyrate and hydrocortisone are interchangeable.

An Obviousness Rejection Must Be Based On
References From The Field Of The Applicant's Endeavor
Or From A Field "Reasonably Pertinent" To The
Particular Problem At Hand

A *prima facie* case must be established using references in the field of applicant's endeavor or a field "reasonably pertinent" to the particular problem with which the inventor was concerned. *See e.g., In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992) ("In order to rely on a reference…, the reference must either be in the field of applicant's endeavor or, if not, then reasonably pertinent to the particular problem with which the inventor was concerned."); *In re Deminski*, 796 F.2d 436 (Fed. Cir., 1986); *Wang Laboratories Inc. v. Toshiba Corp.*, 993 F.2d 858 (Fed. Cir., 1993).

In the instant case, the claimed invention shows how to stabilize an eczema cream. In contrast, Grinstaff teaches a synthetic blood substitute. No evidence of record shows that these two fields are the same. Further, no evidence of record shows that blood substitutes are "reasonably pertinent" to eczema creams.

Where a prior art teaches the same composition as is claimed, a test for whether the reference is from a "reasonably pertinent" art is whether the reference teaches the composition as used in the same *structure*, for the same *purpose*, under the same *conditions*. *See In re Clay*, 966 F.2d 656, 659 (Fed. Cir., 1992) ("A reference may be reasonably pertinent if, even thought it may be in a different field from the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem.")

For example, in *Clay*, the inventor noted that industrial storage tanks often have a dead space between the bottom of the tank and the drainage outlet; refined hydrocarbon products are subject to contamination or degradation by having fluid collect in the dead space. The inventor claimed a method for preventing contamination of refined hydrocarbon products by filling the dead space with an inert gel material. The prior art taught to use *the same gel* to reduce the permeability of natural underground hydrocarbon-bearing formations. The

Court of Appeals found the prior art reference was not in an analogous art, because the prior art taught use of the same gel, in a different *structure*, for a different *purpose*, under different *conditions*.

In the instant case, even assuming that the claime dinvention is the same as Griffin's prior art structure, the claimed invention is used in a *different structure* (no shell required) for *a different purpose* (a blood substitute rather than an eczema cream) under *different conditions* (topical rather than intravenous application) than Grinstaff's invention.

The art of record fails to teach a reasonable expectation of success if hydrocortisone 17-butyrate were used in Grinstaff's polymer shells

Reasonable expectation of success is the standard under which obviousness is determined. *See e.g., In re Rinehart*, 531 F.2d 1048 (C.C.P.A., 1976) (unchallenged evidence showed that prior art combination would not work); *Amgen, Inc. v. Chugai Pharmaceutical Co*., 927 F.2d 1200, 1207-08 (Fed. Cir., 1991), *certiorari denied*, 502 U.S. 856.

In the instant case, the prior art fails to provide a "reasonable expectation of success" if hydrocortisone 17-butyrate were included in Grinstaff's microcapsule delivery system. To the contrary, Grinstaff teaches a reasonable expectation of failure.

Grinstaff teaches that his micro spheres are admirably stable. Grinstaff, at 34:53 to 35:22, notes that at body temperature, his micro spheres

survive intact for at least a month. Grinstaff, at 38:5-36, teaches that to liberate drug contained in the micro spheres, one must dissolve the micro spheres with an organic solvent (Grinstaff uses mercaptoethanol). Grinstaff thus teaches that when a drug or medical imaging agent is included in his micro spheres, the spheres survive intact for at least a month before opening and releasing the drug.

This may be quite advantageous when administering a medical imaging agent. This would, however, render a topical medicine like hydrocortisone 17-butyrate inoperable. Adding hydrocortisone 17-butyrate to Grinstaff's micro spheres would sequester the hydrocortisone 17-butyrate, rendering it unavailable and ineffective.

Further, Grinstaff teaches that the micro spheres would sequester the hydrocortisone 17-butyrate for at least a month. Hydrocortisone 17-butyrate, however, is administered as a *skin cream*; thus, if the patient bathes at least once a month (a likely assumption for a patient who has access to prescription drugs such as hydrocortisone 17-butyrate) the patient would wash away the intact micro spheres - and their drug load - before the drug is released.

A patient could conceivably open the micro spheres by washing the micro sphere-treated skin with an organic solvent such as mercaptoethanol. This would be counter-productive, however, because organic solvent dries and damages skin. Compounding the problem, hydrocortisone 17-butyrate is used to treat

eczema - already sensitive skin - so washing eczema-affected skin with an organic solvent would *exacerbate* the eczema, not ameliorate it.

The absence of an expected property is evidence of non-obviousness

The absence of a property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of non-obviousness. *See Ex parte Mead Johnson & Co.*, 227 U.S.P.Q. 78 (B.P.A.I., 1985).

In the instant case, the prior art teaches that hydrocortisone 17-butyrate degrades into hydrocortisone 21-butyrate. Nothing in the prior art of record contradicts this. Thus, one of skill in the art would have expected that hydrocortisone 17-butyrate, whether or not incorporated into Grinstaff's micro spheres, would degrade into the 21-butyrate form.

In contrast to what the prior art teaches, the inventor has found a way to stabilize hydrocortisone 17-butyrate. The instant Specification shows that after 6 months of storage at 40° C, an eczema skin cream made without added omega-6 acid has 9.17% total impurities (6.36 % hydrocortisone 21-butyrate and 2.81% other impurities), while the same skin cream with added omega-6 acid has only 5.56% total impurities (5.00 % hydrocortisone 21-butyrate and 0.56% other impurities). These results are of both statistical and practical significance. *Cf. Ex parte Gelles*, 22 U.S.P.Q.2d 1318, 1319 (B.P.A.I., 1992).

These results are statistically significant because the difference in results is statistically not likely to be caused by random variation. These results are practically significant because, as the Specification explains at 2:12-14, isomerization is of particular concern to pharmaceutical formulators since the isomerization reaction raises therapeutic and regulatory issues regarding the efficacy and composition of isomerized compositions.

grinstaff fails to show obviousness by "a preponderance of the evidence"

Applicant includes with this Amendment a *Declaration Under 37 C.F.R. § 1.132*. Applicant respectfully believes that this *Declaration* is timely filed because Applicant submits this Declaration before filing a *Notice of Appeal*. *See In re Rothermel*, 276 F.2d 393 (C.C.P.A., 1960).

Applicant respectfully notes that to reject an application as obvious, it is not enough that *some* evidence may tend to show that the invention is obvious. Rather, non-patentability must be shown by a "preponderance" of the evidence. *E.g., In re Oetiker*, 977 F.2d 1443 (Fed. Cir., 1992). This legal standard requires not only that there be *evidence* showing obviousness, but that the evidence showing obviousness be *more convincing* than any countermanding evidence. *Id.*

In the instant case, the evidence showing obviousness is not more convincing than the countermanding evidence. To the contrary, the evidence ostensibly showing obviousness - Grinstaff *et al.* - by its own terms shows that the

combination would not be operable, and thus shows that the claimed invention is non-obvious.

Applicant therefore respectfully believes that this application is in condition for prompt allowance.

Respectfully submitted on behalf of the Applicant by its attorneys,
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Enclosures
Petition for Extension of Time with appurtenant government filing fee.
Pravin M. Patel, *Declaration Under 37 C.F.R. § 1.132* (December 2007)
Replacement Power of Attorney
Assignment

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